REMARKS

Claims 1-12 and 20-30 stand rejected under 35 U.S.C. §112, first paragraph, and claims 20, 25 and 26 are rejected under 35 U.S.C. §103(a). For reasons set forth in detail below, Applicant requests that the rejections be withdrawn and the claims be allowed to issue.

1. THE REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1, 5, 9 and 20-25 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that the claims encompass subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to the Examiner, the claims are drawn to a product or method for reducing ß-cell dysfunction in an individual with a pancreatic disorder comprising administering a nucleic acid encoding any IL-1 ß inhibitor, or any inhibitor of Fas mediated apoptosis; however, a broad genus of inhibitors have not been described in the specification. The Examiner alleges that applicants do not describe the nucleotide sequences referred to in the specification which includes mutant forms of Fas or FADD protein, members of the bcl-2 family, etc. The Examiner maintains that with the exception of the IL-1β inhibitors such as IL-1Ra, IGF-1 and IRAP wherein nucleotides sequences are known in the art and are known to be IL-1β inhibitors, the application does not meet the written description provisions of 35 U.S.C. §112, first paragraph.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can

reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111, (Fed. Cir. 1991). Possession may be shown in a variety of different ways, including description of an actual reduction to practice, or by a showing that the invention was "ready for patenting" such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.* 525 U.S. 55, 68,119 S. Ct. 304, 48 USPQ2d 1641 (1998).

Moreover, as set forth in the Written Description Guidelines for examination of patent applications, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus."(see, MPEP 2100-164)

Applicants assert that the essential feature of the present invention is based on the discovery that inhibition of IL-1β activity, or Fas-mediated apoptosis, reduces pancreatic β-cell dysfunction. Thus, the present invention relates to methods of reducing ß-cell dysfunction comprising introduction of a nucleic acid molecule encoding an inhibitor of IL-1ß or FAS mediated apoptosis into a pancreatic ß-cell. For purposes of

the present invention, any nucleic acid molecule capable of encoding an inhibitor of IL-1ß or FAS mediated apoptosis may be utilized to reduce β-cell dysfunction.

As set forth in the working examples of the specification expression of two IL-1β inhibitors, interleukin-1 receptor antagonist protein (IL-IRa) and human insulin-like growth factor-I (IGF-1), were capable of reducing ß-cell dysfunction and/or apoptosis. In addition, Applicants disclose a number of different species of inhibitors of IL-1ß activity including NF-KB inhibitors, STATS, STAT6 and NF-AT, as well as inhibitors of FAS mediated apoptosis. Furthermore, the specification unmistakably informs one skilled in the art that such inhibitors can be identified by their ability to (i) inhibit insulin release from ß-cells in the presence of IL-1ß and/or (ii) their ability to inhibit nitric oxide production in the presence of IL-1ß. Given the teaching of such distinguishing characteristics associated with the species of IL-1ß inhibitors, one skilled in the art could determine whether a given composition functioned as an IL-1ß inhibitor.

Applicants assert that given the teaching in the specification that IL-1β inhibitors can reduce β cell dysfunction, in combination with working examples demonstrating such activity, one skilled in that art would reasonably recognize that Applicants were indeed in possession of the invention.

Claims 1-12 and 20-30 stand rejected under 35 U.S.C.§112 first paragraph. The Examiner alleges that applicants did not teach one of skill in the art how to make and use the invention claimed. The Examiner maintains that *in vitro* administration of vectors comprising the aforesaid nucleic acids to human islet cells,

wherein successful expression occurs as by glucose measurements and NO production, cannot be extrapolated to that which occurs *in vivo*.

In this regard, the Examiner's attention is respectfully directed to the Rule 132 Declaration of Dr. Paul Robbins ("the Declaration"), attached herewith as Exhibit A. The experiments described in the Declaration were conducted to demonstrate that recombinant expression of an IL-1β inhibitor, in pancreatic islet β-cells, could reduce pancreatic islet β-cell dysfunction ***in vivo***. The experiments were conducted in the NOD mouse model system, wherein the NOD strain of mice is susceptible to autoimmune mediated diabetes.

As set forth in the Declaration, pancreatic islet β-cells were derived from NOD mice and transfected with recombinant adenovirus or lentivirus vectors expressing either a control LacZ gene (Ad-LacZ or LtV-LacZ) or the interleukin-1 receptor antagonist protein (IRAP) (Ad-IRAP or LtV-IRAP). IRAP is known to be an inhibitor of IL-1β activity (¶4 of the Declaration).

A total of approximately 400 transduced pancreatic islet β-cells were then transplanted into streptozotocin treated NOD mice; 200 control lacZ transduced islets transplanted under one kidney capsule and 200 IRAP transduced islets transplanted under the opposite kidney capsule. Streptozotocin is a compound which is known to selectively kill pancreatic islet β-cells. Thus, the experiment is designed to test the protection afforded to pancreatic islet β-cells expressing an inhibitor of IL-1β activity, *i.e.*, IRAP, when transplanted into an animal model susceptible to development of diabetes (¶5 of the Declaration).

When the transplanted animals began to show signs of diabetes, the animals were sacrificed and the histology of the transplanted cells was examined. Figures 2 and 3 show that Ad-IRAP and LtV-IRAP, respectively, are capable of reducing islet destruction in transplanted NOD mice. Panels A and B are stained for insulin, using anti-insulin antibodies, and demonstrate greater insulin expression in the animals receiving transplanted pancreatic islet β-cells transfected with vectors expressing IRAP (Ad-IRAP and LtV-IRAP) versus control cells (Ad-LacZ and LtV-LacZ). In addition, as depicted in panels C and D there is less white blood cell infiltration around the islets in the animals receiving cells expressing IRAP. Thus, the data depicted in Figures 2 and 3 demonstrate that expression of an IL-1β inhibitor is capable of reducing *in vivo* pancreatic islet β-cell destruction (¶6 of the Declaration).

In a second set of experiments, NOD animal derived pancreatic islet β-cells were transfected with recombinant adenovirus vectors genetically engineered to express the LacZ, or IRAP genes. The transfected islet cells were then transplanted into streptozotocin treated NOD *SCID* mice (Figure 4). As indicated above, such mice do not have functional pancreatic islet β-cells due to streptozotocin mediated destruction. In addition, since the mice are *SCID* mice, they do not have a functional immune system. Once the transfected pancreatic islet β-cell had been transplanted into the NOD SCID animals, the animals were challenged with spleen cells derived from an diabetic mouse. Such spleen cells will contain a population of T lymphocytes primed to attack pancreatic islet β-cells (¶7 of the Declaration).

Figure 5 of the Declaration is a summary of the data derived from the T-lymphocyte challenged transplants. The data is presented as number of survival days following T-lymphocyte challenge where n represents the number of animals studied. As indicated, the animals expressing IRAP survived for longer periods of time than the controls, *i.e.*, 37 days (Ad-IRAP) versus 27 days (Ad-LacZ). Thus, the data indicates *in vivo* reduction in pancreatic islet cell destruction in animals expressing an inhibitor of IL-1β activity (¶8 of the Declaration).

Applicants maintain that based on the *in vivo* data presented herein, coupled with the instant specification which discloses (i) specific regulators of IL-1β activity (see, page 15, line 1 through page 16, line 4 of the specification) and inhibitors of FasL triggered apoptosis (see, page 16, lines 5-17 of the specification); (ii) methods for deriving nucleic acid molecules encoding such regulators and inhibitors (see, page 18, line 3 through page 19, line);(iii) recombinant expression vectors that can be utilized to express such nucleic acid molecules (see, page 19, line 8 through page 23, line 7 of the specification); and (iv) methods for transfer and expression of nucleic acid molecules into pancreatic β-cells (see, page 23, line 10 through page 27, line 11 of the specification), one skilled in the art could, without undue experimentation, practice the claimed methods of the invention. All that is required is that the skilled artisan, follow the teachings of the specification.

In view of the foregoing remarks, the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

2. THE CLAIMS ARE NOT OBVIOUS

Claims 20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (U.S. Pat. No.: 5,977,341; "Monia '341"), in view of Monia et al. (U.S. Pat. No.: 5,962,673; "Monia "673"), and further in view of Crawford et al. (U.S. 6,107,057; Crawford '057"), and Robbins et al. Claims 20 and 26 are also rejected in view of Crawford et al. (U.S. 6,107,057; Crawford '057"), and Robbins et al.

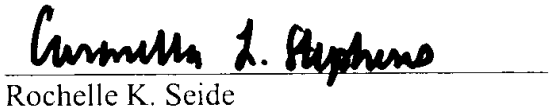
To expedite the allowance of claims, Applicants have cancelled claim 20, 25 and 26 without prejudice to their right to pursue the subject matter encompassed by the cancelled claims in a later application.

CONCLUSION

Attached hereto as APPENDIX A is a marked-up version of the changes made to the claims by the current amendment. Entry of the foregoing amendments and remarks into the file history of the above identified application and reconsideration of the claims is respectfully requested.

Applicants believe that the foregoing amendments and remarks place the claims in condition for allowance. An allowance is earnestly sought.

Respectfully submitted,



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APPENDIX

The claims have been amended as follows:

Cancel claims 20, 25 and 26 without prejudice.